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DOCKET NO. 29191-707

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Jonathan C. Heller et al.		
Serial No.	:	10/645,863	Art Unit:	2855
Filed	:	August 20, 2003	Examiner:	To Be Assigned
For	:	SYSTEM OF ANALYZING COMPLEX MIXTURES OF BIOLOGICAL AND OTHER FLUIDS TO IDENTIFY BIOLOGICAL STATE INFORMATION		

Mail Stop: Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION TO MAKE SPECIAL UNDER 37 C.F.R. § 1.102(d)

Sir:

This is a Petition to Make Special the above-identified patent application. The basis for this petition is that a pre-examination search has been made and Applicants have herein described how the presently claimed subject matter is patentable over the references.

In accordance with the Manual of Patent Examining Procedure § 708.02 VIII, the following is submitted herewith:

A. This Petition to Make Special accompanied by the fee of $130.00 set forth in 37 CFR 1.17(h):

The Commissioner is hereby authorized to charge this fee of $130.00 as well as any other required fees due in connection with this submission, including petition and extension of time fees, to Deposit Account No. 23-2415 (Docket No. 29191-707).

B. Presentation of all claims directed to a single invention:

A complete listing of the pending claims is set forth beginning on page 12 of this paper. If the Office determines that all the claims presented are not obviously directed to as single invention, Applicants will make an election without traverse as a prerequisite to the grant of special status.

C. A statement that a pre-examination search was made, listing the field of search by class and subclass, publication, Chemical Abstracts, foreign patents, etc.

Applicants hereby state that a pre-examination search was made, and provide a listing the field of search by class and subclass, publication, Chemical Abstracts, foreign patents, etc., beginning on page 3 of this paper, along with a listing of the search results. In total, approximately 8,000 patent documents were screened.

D. One copy of each of the references deemed most closely related to the subject matter encompassed by the claims if said references are not already of record:

A set of tabbed binders with a copy of each reference deemed most closely related to the subject matter encompassed by the claims is submitted herewith.

E. A detailed discussion of the references, which discussion points out, with particularity required by 37 CFR 1.111 (b) and (c), how the claimed subject matter is patentable over the references:

A detailed discussion of the references, pointing out, with particularity required by 37 CFR 1.111 (b) and (c), how the claimed subject matter is patentable over the references is provided herewith, beginning on page 17 of this paper.

In view of the submission herewith of the above-noted items, and the discussion that follows, Applicants request that this Petition to Make Special be granted and the examination of the application be advanced.

Searches:

Journal Articles:

Searches Conducted

The search covered the holdings at the Harvard Medical School library, select literature at the MIT library, and other relevant resources spanning the ten-year period between 1993 and 2003. Journal articles, monographs, conference proceedings, reference handbooks, and dissertations were reviewed. The manual search was augmented by database searching, covering work by key researchers and organizations.

Search Results:

Adam et al., "Serum Protein Fingerprinting Coupled with a Pattern-matching Algorithm Distinguishes Prostate Cancer from Benign Prostate Hyperplasia and Healthy Men", Cancer Research, Vol. 62, pp. 3609-3614 (2002). (Previously cited in IDS.)

Bañez et al., "Diagnostic Potential of Serum Proteomic Patterns in Prostate Cancer", The Journal of Urology, Vol. 170, pp. 442-446 (2003).

Billingsley, J., "Research offers hope in fight against ovarian cancer", USA Today.com, 3 pages (February 2002).

Cazares et al., "Normal, Benign, Preneoplastic, and Malignant Prostate Cells Have Distinct Protein Expression Profiles Resolved by Surface Enhanced Laser Desorption/Ionization Mass Spectrometry", Clinical Cancer Research, Vol. 8, pp. 2541-2552 (2002).

CBS News, "Setback For A Silent Killer", CBSNews.com, 2 pages (February 2002).

Etzioni et al., "Combining biomarkers to detect disease with application to prostate cancer", Biostatistics, Vol. 4:4, pp. 523-538 (2003).

Geracimos, A., "Outwitting Ovarian Cancer", The Washington Times, 4 pages (April 2002).

Haran, C., "The Promise of Proteins – Do These Tricky Molecules Hold the Answers To Cancer?", pp. 43-47 (2003).

Henry, C., "Diagnosing Ovarian Cancer – Proteomics shows promise for early detection of deadly disease", C&EN, page 13 (2002).

Hilario et al., "Machine learning approaches to lung cancer prediction from mass spectra", Proteomics, Vol. 3, pp. 1716-1719 (2003).

Hollon, T., "Software Zeroes In on Ovarian Cancer", The Scientist, Vol. 16:8, 5 pages (2002).

Johannes, L., "Tiny Protein May Lead To Better Screen Test For Prostate Cancer", The Wall Street Journal, 2 pages (November 2003).

Levine, P., "Correlogic's Ovarian Cancer Test Nears Market Introduction", Diagnostic Testing and Technology Report, Vol. III, No. 11, pp. 5-7 (2003).

Liotta et al., "Written in Blood", Nature, Vol. 425, p. 905 (2003).

Markey et al., "Decision tree classification of proteins identified by mass spectrometry of blood serum samples from people with and without lung cancer", Proteomics, Vol. 3, pp. 1678-1679 (2003).

Mian et al., "A prototype methodology combining surface-enhanced laser desorption/ionization protein chip technology and artificial neural network algorithms to predict the

chemoresponsiveness of breast cancer cell lines exposed to Paclitaxel and Doxorubicin under *in vitro* conditions", Proteomics, Vol. 3, pp. 1725-1737 (2003).

Miller et al., "Antibody microarray profiling of human prostate cancer sera: Antibody screening and identification of potential biomarkers", Proteomics, Vol. 3, pp. 56-63 (2003).

Neville et al., "Generalizable mass spectrometry mining used to identify disease state biomarkers from blood serum", Proteomics, Vol. 3, pp. 1710-1715 (2003).

Petricoin III et al., "Serum Proteomic Patterns for Detection of Prostate Cancer", Journal of the National Cancer Institute, Vol. 94:20, pp. 1576-1578 (2002). (Previously cited in IDS.)

Petricoin III et al., "Use of proteomic patterns in serum to identify ovarian cancer", The Lancet, Vol. 359, pp. 572-577 (2002). (Previously cited in IDS.)

Purohit et al., "Discriminant models for high-throughput proteomics mass spectrometer data", Proteomics, Vol. 3, pp. 1699-1703 (2003).

Qu et al., "Boosted Decision Tree Analysis of Surface-Enhanced Laser Desorption/Ionization Mass Spectral Serum Profiles Discriminates Prostate Cancer from Non-cancer Patients", Clinical Chemistry, Vol. 48:10, pp. 1835-1843 (2002).

Rubin, R., "Blood test may spot ovarian cancer earlier", USA Today.com, 2 pages (February 2002).

Service, R., "Recruiting Genes, Proteins For a Revolution in Diagnostics", Science, Vol. 300, pp. 236-239 (2003). (Previously cited in IDS.)

Somorjai et al., "Class prediction and discovery using gene microarray and proteomics mass spectroscopy data: curses, caveats, cautions", Bioinformatics, Vol. 19:12, pp. 1484-1491 (2003).

Sorace et al., "A data review and re-assessment of ovarian cancer serum proteomic profiling", BMC Bioinformatics, Vol. 4:24, 13 pages (2003).

Tatay et al., "Multiple approaches to data-mining of proteomic data based on statistical and pattern classification methods", Proteomics, Vol. 3, pp. 1704-1709 (2003).

Tirumalai et al., "Characterization of the Low Molecular Weight Human Serum Proteome", Molecular & Cellular Proteomics, Vol. 2:10, pp. 1096-1103 (2003).

Touchette, N., "Diagnosing Ovarian Cancer by Proteomics", Genome News Network, 2 pages (November 2003).

Vlahou et al., "Development of a Novel Proteomic Approach for the Detection of Transitional Cell Carcinoma of the Bladder in Urine", American Journal of Pathology, Vol. 158:4, pp. 1491-1502 (2001).

Wang et al., "Analysis of human serum proteins by liquid phase isoelectric focusing and matrix-assisted laser desorption/ionization-mass spectrometry", Proteomics, Vol. 3, pp. 1661-1666 (2003).

Wright, Jr. et al., "Proteinchip surface enhanced laser desorption/ionization (SELDI) mass spectrometry: a novel protein biochip technology for detection of prostate cancer biomarkers in complex protein mixtures", Prostate Cancer and Prostatic Diseases, Vol. 2, pp. 264-276 (1999).

Wu et al., "Comparison of statistical methods for classification of ovarian cancer using mass spectrometry data", Bioinformatics, Vol. 19:13, pp. 1636-1643 (2003).

Yanagisawa et al., "Proteomic patterns of tumour subsets in non-small-cell lung cancer", The Lancet, Vol. 362, pp. 433-439 (2003).

Yasui et al., "A data-analytic strategy for protein biomarker discovery: profiling of high-dimensional proteomic data for cancer detection", Biostatistics, Vol. 4:3, pp. 449-463 (2003).

Zhu et al., "Tree-based disease classification using protein data", Proteomics, Vol. 3, pp. 1673-1677 (2003).

U.S. Patents/Publications:

Searches Conducted

The search included manual review of US patent conducted at the USPTO and covered filings spanning the ten-year period between 1993 and 2003, including review of filings contained within US patent class 600/300, as well as tracing key assignee and inventor filing histories and citation analysis of key findings.

The manual searches were augmented by database searching, covering work by key companies and inventors, including the following keyword searches:

- ("Business method") AND ("MS" OR "mass spec" OR "mass spectrometry") AND (phenotypic OR phenotype OR disease OR population OR "multiple samples") AND diagnostic
- (business <near> method) AND diagnostic AND ("mass spectrometry") AND kit
- (Business) AND ("MS" OR "mass spec" OR "mass spectrometry") AND (phenotypic OR phenotype OR disease OR population OR "multiple samples") AND diagnostic

Search Results

Chen et al., US 2003/0153007, Published August 14, 2003, Class 435, Subclass 7.1, "Automated Systems and Methods for Analysis of Protein Post-Translational Modification."

Gavin et al., US 2002/0193950 A1, Published December 19, 2002, Class 702, Subclass 28, "Method For Analyzing Mass Spectra."

Hitt et al., US 2003/0004402, Published January 2, 2003, Class 600, Subclass 300, "Process for Discriminating Between Biological States Based on Hidden Patterns From Biological Data."

Kristal et al., U.S. Patent No. 6,558,955 B1, Issued May 6, 2003, Class 436, Subclass 63, "Methodology for Predicting And/Or Diagnosing Disease."

Lubman et al., US 2002/0039747, Published April 4, 2002, Class 435, Subclass 7.1, "Mapping of Differential Display of Proteins." (Previously cited in IDS.)

Mischak et al., US 2003/0132114 A1, Published July 17, 2003, Class 204, Subclass 452, "Method and Device for the Qualitative and/or Quantitative Analysis of a Protein and/or Peptide Pattern of a Liquid Sample That Is Derived From the Human or Animal Body."

Parish et al., US 2004/0029194, Published February 12, 2004, Class 435, Subclass 7.23, "Method of Identifying Cancer Markers and Uses Therefor in the Diagnosis of Cancer."

Patz, Jr. et al., US 2003/0013120, Published January 16, 2003, Class 435, Subclass 7.1, "System and Method for Differential Protein Expression and a Diagnostic Biomarker Discovery System and Method Using Same."

Patz, Jr. et al., US 2004/0005634, Published January 8, 2004, Class 435, Subclass 7.1, "System and Method for Determining Differential Protein Expression, Diagnostic Biomarker Discovery System and Method of Using the Same, and Protein Biomarkers and Therapeutic and Diagnostic Uses Thereof."

Paulse et al., US 2002/0138208 A1, Published September 26, 2002, Class 702, Subclass 22, "Method for Analyzing Mass Spectra."

Slepnev, V., US 2003/0077611, Published April 24, 2003, Class 435, Subclass 6, "Methods and Systems for Dynamic Gene Expression Profiling."

van der Greef et al., US 2003/0134304, Published July 17, 2003, Class 435, Subclass 6, "Method and System for Profiling Biological Systems."

Wan et al., US 2003/0148295, Published August 7, 2003, Class 435, Subclass 6, "Expression Profiles and Methods of Use."

Wright et al., US 2003/0228639, Published December 11, 2003, Class 435, Subclass 7.23, "Prostate Cancer Markers."

Foreign Patents/Publications:

Searches Conducted

A manual search of European patent documents (EP, PCT, DE and GB) was performed, covering relevant patent classes and filings spanning a ten-year period between 1993 and 2003. The European patent searches included similar keyword, assignee, and inventor searches as that used with respect to the US searches, as well as covering filings of the following IPCs:

- G01N 33/00, 48, 483, 487, 497, 50, 54, 68
- C12Q 1/68, 70
- G06F 19/00
- G01N 1/00, 24/00, 53, 574
- C07H 21/00

Search Results

Aguilera et al., WO 03/042774 A2, Published May 22, 2003, Intl. Class G06F (no subclass), "Mass Intensity Profiling System and Uses Thereof."

Blagoev et al., WO 03/038055 A2, Published May 8, 2003, Intl. Class C12N (no subclass), "Proteins Involved in Regulation of Adipocytes and Uses Related Thereto."

Brame et al., WO 03/014302 A2, Published February 20, 2003, Intl. Class C12N, (no subclass), "Detection of Differential Expression of Protein Using Gel-Free Proteomics."

Chan et al., WO 03/091695 A2, Published November 6, 2003, Intl. Class G01N (no subclass), "Identification of Biomarkers for Detecting Prostate Cancer."

Dasseux et al., WO 02/04957 A2, Published January 17, 2002, Intl. Class G01N, Subclass 33/68, "Fourier Transform Mass Spectrometry of Complex Biological Samples."

Emili et al., WO 02/097703 A2, Published December 5, 2002, Intl. Class G06F, Subclass 19/00, "Protein Expression Profile Database."

Gavin et al., WO 03/031031 A1, Published April 17, 2003, Intl. Class B01D, Subclass 59/44, "Method For Analyzing Mass Spectra."

Goodnough, D., WO 01/57518 A2, Published August 9, 2001, Intl. Class G01N, Subclass 33/00, "Method of Non-Targeted Complex Sample Analysis."

Hitt et al., WO 02/06829 A2, Published January 24, 2002, Intl. Class G01N, Subclass 33/48, "A Process for Discriminating Between Biological States Based on Hidden Patterns from Biological Data." (Previously cited in IDS.)

Margus et al., WO 03/083442 A2, Published October 9, 2003, Intl. Class G01N (no subclass), "Life Sciences Business Systems and Methods."

Parish et al., WO 02/08760 A1, Published January 31, 2002, Intl. Class G01N, Subclass 33/54, "Method of Identifying Cancer Markers and Uses Therefor in the Diagnosis of Cancer."

Watkins, B., WO 01/36977 A2, Published May 25, 2001, Intl. Class G01N, Subclass 33/574, "Methods and Compositions for Identifying Disease Markers."

Yip et al., WO 01/25791 A2, Published April 12, 2001, Intl. Class G01N, Subclass 33/574, "Prostate Cancer Marker Proteins."

Complete Listing of the Pending Claims:

1. (Previously presented) A business method comprising:
    a) collecting more than 10 case samples representing a clinical phenotypic state and more than 10 control samples representing patients without said clinical phenotypic state;
    b) using electrophoresis followed by a mass spectrometry platform system to obtain mass spectral data in said case samples and in said control samples without regard to a specific identity of at least some of said spectral components;
    c) identifying representative patterns of markers that distinguish datasets from case samples and control samples wherein said patterns contain more than 15 markers that are represented on output of said mass spectrometer, but the identity of at least some of said more than 15 markers is not known;
    d) marketing diagnostic products that use said representative patterns to identify said phenotypic state with a disposable device; and
    e) selling said disposable device.

2. (Canceled).

3. (Previously presented) The method as recited in claim 1 wherein said products are marketed in a clinical reference laboratory.

4. (Previously presented) The method as recited in claim 1 wherein said marketing step markets kits.

5. (Original) The method as recited in claim 3 wherein said kits are FDA approved kits.

6. (Previously presented) The method as recited in claim 1 wherein said phenotypic state is a drug response phenotype and further comprising the step of collecting a royalty on said drug.

7. (Previously presented) The method as recited in claim 1 further comprising the step of collecting said samples in collaboration with a collaborator.

8. (Original) The method as recited in claim 7 wherein said collaborator is an academic collaborator.

9. (Original) The method as recited in claim 7 wherein said collaborator is a pharmaceutical company.

10. (Original) The method as recited in claim 9 wherein said pharmaceutical company collects said samples in a clinical trial.

11. (Previously presented) The method as recited in claim 10 wherein said patterns are used to segregate a drug response phenotype.

12. (Original) The method as recited in claim 11 further comprising the step of collecting royalties on said drug.

13. (Original) The method as recited in claim 11 wherein the step of marketing diagnostic products is performed by the same company as the company performing the identifying step.

14. (Previously presented) The method as recited in claim 1 wherein data from one of said samples are being processed computationally while another of said samples are in said mass spectrometry platform.

15. (Original) The method as recited in claim 1 wherein said markers are polypeptides.

16. (Original) The method as recited in claim 1 wherein said markers are proteins.

17. (Previously presented) The method as recited in claim 15 wherein said patterns contain more than 30 polypeptides that are represented on output of said mass spectrometer, but the identity of at least some of said more than 30 polypeptides is not known.

18. (Previously presented) The method as recited in claim 15 wherein said patterns contain more than 50 polypeptides that are represented on output of said mass spectrometer, but the identity of at least some of said more than 50 polypeptides is not known.

19. (Previously presented) The method as recited in claim 15 wherein said patterns contain more than 100 polypeptides that are represented on output of said mass spectrometer, but the identity of at least some of said more than 100 polypeptides is not known.

20. (Previously presented) The method as recited in claim 15 wherein said samples contain more than 1000 polypeptides that are represented on output of said mass spectrometer, but the identity of at least some of said more than 1000 polypeptides is not known.

21. (Previously presented) The method as recited in claim 1 wherein said marketing step markets a mass spectrometry system used to identify said representative states in patient samples.

22. (Previously presented) The method as recited in claim 1 wherein more than 50 of said cases samples and 50 of said control samples are used.

23. (Previously presented) The method as recited in claim 1 wherein more than 100 of said case samples and 100 of said control samples are used.

24. (Previously presented) The method as recited in claim 1 wherein said diagnostic products use said mass spectrometry platform.

25. (Previously presented) The method as recited in claim 1 wherein said step of using a mass spectrometry platform is preceded by the step of preparing said samples on a microfluidics device.

26. (Original) The method as recited in claim 25 wherein said diagnostic products are marketed with a disposable microfluidics device, said disposable microfluidics device processing diagnostic samples for use in said mass spectrometry platform.

27. (Original) The method as recited in claim 25 wherein said microfluidics device comprises a separations device.

28. (Original) The method as recited in claim 25 wherein said microfluidics device removes high abundance common proteins.

29. (Previously presented) The method as recited in claim 1 wherein said mass spectrometry platform is a time of flight mass spectrometer.

30. (Previously presented) The method as recited in claim 1 wherein said mass spectrometer is a Hadamard time of flight mass spectrometer.

31. (Previously presented) The method as recited in claim 1 wherein said diagnostic products are marketed by a diagnostic partner.

32. (Previously presented) The method as recited in claim 1 wherein said phenotype is a drug response phenotype.

33. (Previously presented) The method as recited in claim 1 wherein said phenotype is a drug resistance phenotype.

34. (Previously presented) The method as recited in claim 1 wherein said phenotype is a disease stage phenotype.

35. (Previously presented) The method as recited in claim 1 wherein said phenotype is a disease recurrence phenotype.

36. (Previously presented) The method as recited in claim 1 wherein said phenotype is a disease state phenotype.

37. (Previously presented) The method as recited in claim 1 wherein said phenotype is a treatment selection phenotype.

38. (Previously presented) The method as recited in claim 1 wherein said phenotype is a disease diagnostic phenotype.

39. (Previously presented) The method as recited in claim 1 wherein said phenotype is a drug toxicity phenotype.

40. (Previously presented) The method as recited in claim 1 wherein said phenotype is an adverse drug response phenotype.

41. (Original) The method as recited in claim 25 wherein said microfluidics device comprises an electrospray source.

42. (Previously presented) The method as recited in claim 1 wherein said samples contain complex mixtures of polypeptides.

43. (Previously presented) The method as recited in claim 1 wherein revenue is derived from sales of microfluidics devices, mass spectrometers, informatics tools, patterns and/or computer programs for classifying samples and/or from services that provide diagnostic information and/or pattern discovery and/or validation.

Discussion:

Of the pre-examination search results, the following references are deemed most closely related to the claimed subject matter. The claimed subject matter is patentable over each of these references, as discussed below. It is to be understood that this discussion assumes the references are prior art, but no admission is made that any discussed reference is prior art material to patentability as defined in §1.56. Applicants reserve the right to further establish the patentability of the claimed invention over any of the references discussed herewith, and/or to prove that a reference may not be prior art, and/or to prove that a reference may not be enabling for the teachings purportedly offered.

The Adam et al. article, "Serum Protein Fingerprinting Coupled with a Pattern-matching Algorithm Distinguishes Prostate Cancer from Benign Prostate Hyperplasia and Healthy Men", Cancer Research, Vol. 62, pp. 3609-3614 (2002), describes using a protein biochip surface enhanced laser desorption/ionization mass spectrometry approach with a pattern-matching algorithm to distinguish prostate cancer from benign prostate hyperplasia and healthy men, but does not teach the invention, for example, as recited in claim 1. For instance, the Adam article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Bañez et al. article, "Diagnostic Potential of Serum Proteomic Patterns in Prostate Cancer", The Journal of Urology, Vol. 170, pp. 442-446 (2003), discusses the diagnostic potential of serum proteomic patterns obtained from surface enhanced laser desorption/ionization time of flight mass spectrometry in detecting prostate cancer, but does not teach the invention, for example, as recited in claim 1. For instance, the Bañez article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Blagoev et al. application, WO 03/038055 A2, Published May 8, 2003, Intl. Class C12N (no subclass), "Proteins Involved in Regulation of Adipocytes and Uses Related Thereto", discusses proteins involved in adipocyte regulation as well as methods of conducting drug or target discovery businesses, but does not teach the invention, for example, as recited in claim 1. For instance, the Blagoev application does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples. Accordingly, one or more of steps a) to e) are not taught, for example.

The Cazares et al. article, "Normal, Benign, Preneoplastic, and Malignant Prostate Cells Have Distinct Protein Expression Profiles Resolved by Surface Enhanced Laser Desorption/Ionization Mass Spectrometry", Clinical Cancer Research, Vol. 8, pp. 2541-2552 (2002), discusses using combinations of protein biomarkers resolved by surface enhanced laser desorpton/ionizaton mass spectrometry to differentiate malignant and non-malignant cell populations, but does not teach the invention, for example, as recited in claim 1. For instance, the Cazares article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Chen application, US 2003/0153007, Published August 14, 2003, Class 435, Subclass 7.1, "Automated Systems and Methods for Analysis of Protein Post-Translational Modification", discusses systems and methods applying mass spectrometry to the analysis of peptides and amino acids, particularly to detect phosphorylation patterns, as well as business methods to identify a compound that modulates an amino acid of a target polypeptide or to identify the polypeptide and the nature of the induced modification, and licensing rights for further development of the compound. Nonetheless, the Chen application does not teach the invention, for example, as recited in claim 1. For instance, the Chen application does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers

to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Dasseux et al. application, WO 02/04957 A2, Published January 17, 2002, Intl. Class G01N, Subclass 33/68, "Fourier Transform Mass Spectrometry of Complex Biological Samples", discusses methods for high information content analysis or screening of complex biological systems using Fourier transform mass spectrometry, but does not teach the invention, for example, as recited in claim 1. For instance, the Dasseux application does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Emili et al. application, WO 02/097703 A2, Published December 5, 2002, Intl. Class G06F, Subclass 19/00, "Protein Expression Profile Database", describes the use of peptide profiling to identify, characterize, and classify biological samples, where the correct sequence of the peptide is established through comparisons with genome sequence databases, to create a protein expression profile database. Nonetheless, the Emili application does not teach the invention, for example, as recited in claim 1. For instance, the Emili application does not teach using representative patterns of markers that distinguish datasets from case samples and control samples wherein the patterns contain more than 15 markers, the identity of at least some of which is not known. Accordingly, one or more of steps a) to e) are not taught, for example.

The Gavin et al. US application, US 2002/0193950, Published December 19, 2002, Class 702, Subclass 28, "Method for Analyzing Mass Spectra", discusses using a digital computer to analyze mass spectra by entering a data set obtained from mass spectra from a plurality of samples, each sample assigned a class characterized by a different biological status and forming a classification model that discriminates between classes. Nonetheless, the Gavin application does not teach the invention, for example, as recited in claim 1. For instance, the Gavin application does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers to identify a phenotypic state with a disposable device nor, for

example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Hilario et al. article, "Machine learning approaches to lung cancer prediction from mass spectra", Proteomics, Vol. 3, pp. 1716-1719 (2003), discusses the use of machine learning approaches to identify the most discriminant protein peaks for predicting lung cancer from protein mass spectra, but does not teach the invention, for example, as recited in claim 1. For instance, the Hilario article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers, but the identity of at least some of the more than 15 markers is not known, to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Hitt et al. application, US 2003/0004402, Published January 2, 2003, Class 600, Subclass 300, "Process for Discriminating Between Biological States Based on Hidden Patterns From Biological Data", describes determining a biological state by discovering and analyzing hidden discriminatory biological data patterns, but does not teach the invention, for example, as recited in claim 1. For instance, the Hitt application does not teach using representative patterns of markers that distinguish datasets from case samples and control samples wherein the patterns contain more than 15 markers. Accordingly, one or more of steps a) to e) are not taught, for example.

The Lubman et al. application, US 2002/0039747, Published April 4, 2002, Class 435, Subclass 7.1, "Mapping of Differential Display of Proteins", discusses methods for displaying differential protein expression between two samples, in particular to map differential expression of proteins in non-cancerous, pre-cancerous, and cancerous cells, but does not teach the invention, for example, as recited in claim 1. For instance, the Lubman application does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Markey et al. article, "Decision tree classification of proteins identified by mass spectrometry of blood serum samples from people with and without lung cancer", Proteomics, Vol. 3, pp. 1678-1679 (2003), discusses a classification and regression tree model of proteins identified by mass spectrometry of blood serum samples from people with and without lung cancer, but does not teach the invention, for example, as recited in claim 1. For instance, the Markey article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Mian et al. article, "A prototype methodology combining surface-enhanced laser desorption/ionization protein chip technology and artificial neural network algorithms to predict the chemoresponsiveness of breast cancer cell lines exposed to Paclitaxel and Doxorubicin under *in vitro* conditions", Proteomics, Vol. 3, pp. 1725-1737 (2003), discusses using surface enhanced laser desorption/ionization and artificial neural network algorithms to predict chemoresponsiveness of breast cancer cell lines *in vitro*, but does not teach the invention, for example, as recited in claim 1. For instance, the Mian article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Miller et al. article, "Antibody microarray profiling of human prostate cancer sera: Antibody screening and identification of potential biomarkers", Proteomics, Vol. 3, pp. 56-63 (2003), discusses using antibody microarrays to profile human sera for identifying protein biomarkers having different levels between prostate cancer samples and controls, but does not teach the invention, for example, as recited in claim 1. For instance, the Miller article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers

to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Mischak et al. application, US 2003/0132114, Published July 17, 2003, Class 204, Subclass 452, "Method and Device for the Qualitative and/or Quantitative Analysis of a Protein and/or Peptide Pattern of a Liquid Sample That is Derived From the Human or Animal Body", discusses devices and methods in which proteins and peptides of a liquid sample are separated by capillary electrophoresis, then directly ionized and transferred for analysis online via an interface to a mass spectrometer to give a "fingerprint" describing the overall condition of a human or animal body. Nonetheless, the Mischak application does not teach the invention, for example, as recited in claim 1. For instance, the Mischak application does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Neville et al. article, "Generalizable mass spectrometry mining used to identify disease state biomarkers from blood serum", Proteomics, Vol. 3, pp. 1710-1715 (2003), discusses mining mass spectrometry data using out-of-sample cross-validation simulations of logistic regression, binary decision trees, and linear discriminant analysis to identify disease state biomarkers from blood serum, but does not teach the invention, for example, as recited in claim 1. For instance, the Neville article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers, but the identity of at least some of the more than 15 markers is not known, to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Parish et al. US application, US 2004/0029194, Published February 12, 2004, Class 435, Subclass 7.23, "Method of Identifying Cancer Markers and Uses Therefor in the Diagnosis of Cancer", discusses a mass spectrometry-based method of identifying cancer markers and further provides a number of possible cancer markers, but does not teach the invention, for

example, as recited in claim 1. For instance, the Parish application does not teach using representative patterns of markers that distinguish datasets from case samples and control samples. Accordingly, one or more of steps a) to e) are not taught, for example.

The Patz, Jr. et al. application, US 2003/0013120, Published January 16, 2003, Class 435, Subclass 7.1, "System and Method for Differential Protein Expression and a Diagnostic Biomarker Discovery System and Method Using Same", discusses a diagnostic system to discover biomarkers by fractionating protein content, performing mass spectrometry, creating a protein profile and identifying protein patterns associated with biological conditions, but does not teach the invention, for example, as recited in claim 1. For instance, the Patz application does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers, but the identity of at least some of the more than 15 markers is not known, to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Patz, Jr. et al. application, US 2004/0005634, Published January 8, 2004, Class 435, Subclass 7.1, "System and Method for Determining Differential Protein Expression, Diagnostic Biomarker Discovery System and Method of Using the Same, and Protein Biomarkers and Therapeutic and Diagnostic Uses Thereof", discusses a system and method of obtaining and analyzing protein profiles to determine protein patterns associated with clinical parameters and manifestations of disease, such as cancer, but does not teach the invention, for example, as recited in claim 1. For instance, the Patz application does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers, but the identity of at least some of the more than 15 markers is not known, to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Paulse et al. application, US 2002/0138208, Published September 26, 2002, Class 702, Subclass 22, "Method for Analyzing Mass Spectra", discusses using a digital computer to analyze mass spectra by entering a data set obtained from mass spectra from a plurality of

samples, each sample assigned a class characterized by a different biological status and forming a classification model that discriminates between classes. Nonetheless, the Paulse application does not teach the invention, for example, as recited in claim 1. For instance, the Paulse application does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Petricoin III et al. article, "Serum Proteomic Patterns for Detection of Prostate Cancer", Journal of the National Cancer Institute, Vol. 94:20, pp. 1576-1578 (2002), describes the analysis of serum proteomic mass spectra with bioinformatics to detect prostate cancer, but does not teach the invention, for example, as recited in claim 1. For instance, the Petricoin application does not teach using representative patterns of markers that distinguish datasets from case samples and control samples wherein the patterns contain more than 15 markers. Accordingly, one or more of steps a) to e) are not taught, for example.

The Petricoin III et al. article, "Use of proteomic patterns in serum to identify ovarian cancer", The Lancet, Vol. 359, pp. 572-577 (2002), discusses the use of proteomic patterns in serum to distinguish ovarian cancer from non-cancer, but does not teach the invention, for example, as recited in claim 1. For instance, the Petricoin III article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Purohit et al. article, "Discriminant models for high-throughput proteomics mass spectrometer data", Proteomics, Vol. 3, pp. 1699-1703 (2003), discusses using discriminant models to detect differences in protein patterns between mass spectrometer data from healthy and diseased patients, but does not teach the invention, for example, as recited in claim 1. For instance, the Purohit article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the

patterns contain more than 15 markers, but the identity of at least some of the more than 15 markers is not known, to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Qu et al. article, "Boosted Decision Tree Analysis of Surface-Enhanced Laser Desorption/Ionization Mass Spectral Serum Profiles Discriminates Prostate Cancer from Non-cancer Patients", Clinical Chemistry, Vol. 48:10, pp. 1835-1843 (2002), discusses using surface-enhanced laser desorption/ionization, coupled with a bioinformatics learning algorithm, to improve the early detection/diagnosis of prostate cancer, but does not teach the invention, for example, as recited in claim 1. For instance, the Qu article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Sorace et al. article, "A data review and re-assessment of ovarian cancer serum proteomic profiling", BMC Bioinformatics, Vol. 4:24, 13 pages (2003), discusses using mass spectrometry data for serum proteomic profiling with nonparametric statistics and stepwise discriminant analysis to develop rules for diagnosing ovarian cancer, but does not teach the invention, for example, as recited in claim 1. For instance, the Sorace article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers, but the identity of at least some of the more than 15 markers is not known, to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The van der Greef et al. application, US 2003/0134304, Published July 17, 2003, Class 435, Subclass 6, "Method and System for Profiling Biological Systems", describes developing profiles of biological systems based on similarities, differences, and/or correlations between biomolecular components of a single type of a plurality of biological samples, e.g., using hierarchical milti-variate analysis of spectrometric data, but does not teach the invention, for

example, as recited in claim 1. For instance, the van der Greef application does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples. Accordingly, one or more of steps a) to e) are not taught, for example.

The Vlahou et al. article, "Development of a Novel Proteomic Approach for the Detection of Transitional Cell Carcinoma of the Bladder in Urine", American Journal of Pathology, Vol. 158:4, pp. 1491-1502 (2001), discusses using surface enhanced laser desorption/ionization time of flight mass spectrometry for protein profiling to potentially detect transitional cell carcinoma of the bladder in urine, but does not teach the invention, for example, as recited in claim 1. For instance, the Vlahou article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Wan et al. application, US 2003/0148295, Published August 7, 2003, Class 435, Subclass 6, "Expression Profiles and Methods of Use", describes gene expression profiles, microarrays and algorithms, as well as business methods including the marketing, sale, licensing, distribution, screening, or manufacturing in the context of providing customers with gene expression profiles, high information density gene expression profiles and/or protein expression profiles, or determining whether a patient has a disorder associated with overexpression and/or upregulation of a gene. Nonetheless, the Wan application does not teach the invention, for example, as recited in claim 1. For instance, the Wang application does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers, but the identity of at least some of the more than 15 markers is not known, to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Wu et al. article, "Comparison of statistical methods for classification of ovarian cancer using mass spectrometry data", Bioinformatics, Vol. 19:13, pp. 1636-1643 (2003),

compares statistical methods for classifying ovarian cancer using mass spectrometry data, including linear discriminant analysis, quadratic discriminant analysis, *k*-nearest neighbor classifier, bagging and boosting classification trees, support vector machine, and random forest, but does not teach the invention, for example, as recited in claim 1. For instance, the Wu article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers, but the identity of at least some of the more than 15 markers is not known, to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Yanagisawa et al. article, "Proteomic patterns of tumour subsets in non-small-cell lung cancer", The Lancet, Vol. 362, pp. 433-439 (2003), discusses using proteomic patterns of tumor subsets to classify and predict histological groups, nodal involvement and survival in non-small-cell lung cancer, but does not teach the invention, for example, as recited in claim 1. For instance, the Yanagisawa article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Yasui et al. article, "A data-analytic strategy for protein biomarker discovery: profiling of high-dimensional proteomic data for cancer detection", Biostatistics, Vol. 4:3, pp. 449-463 (2003), discusses using surface enhanced laser desorption/ionization mass spectrometry with a data-analytic strategy for discovering protein biomarkers for cancer detection, but does not teach the invention, for example, as recited in claim 1. For instance, the Yasui article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers, but the identity of at least some of the more than 15 markers is not known, to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Yip et al. application, WO 01/25791 A2, Published April 12, 2001, Intl. Class G01N, Subclass 33/574, "Prostate Cancer Marker Proteins", discusses methods and kits that use markers

which are differentially present in samples of prostate cancer patients and subjects who do not have prostate cancer for prostate cancer diagnosis, but does not teach the invention, for example, as recited in claim 1. For instance, the Yip application does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples where the patterns contain more than 15 markers to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

The Zhu et al. article, "Tree-based disease classification using protein data", Proteomics, Vol. 3, pp. 1673-1677 (2003), discusses using tree-bases algorithms to construct an informative classification tree of mass spectrometry protein data that could be used to classify disease status, but does not teach the invention, for example, as recited in claim 1. For instance, the Zhu article does not teach marketing diagnostic products that use representative patterns of markers that distinguish datasets from case samples and control samples to identify a phenotypic state with a disposable device nor, for example, selling the disposable device. Accordingly, one or more of steps a) to e) are not taught, for example.

Conclusion

In view of the foregoing submission, it is respectfully submitted that the application meets the requirements for Special status as defined in 37 CFR 1.102(d) and MPEP 708.02 VIII, and should therefore be granted accelerated examination. Applicants earnestly solicit early examination on the merits and issuance of a Notice of Allowance. Should the Examiner believe that any additional information or amendment is necessary to place the application in condition for allowance, Applicants urge the Examiner to contact the undersigned Attorney via telephone at 650-493-9300.

The Commissioner is hereby authorized to charge any required fees due in connection with this submission, including petition and extension of time fees, and to credit any overpayment, to Deposit Account No. 23-2415 (Docket No. 29191-707).

Respectfully submitted,

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